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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/767,899	BERKA ET AL.
	Examiner	Art Unit
	David C. Thomas	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-44* is/are pending in the application.

4a) Of the above claim(s) *16-21,23 and 35-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-15,22 and 24-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed February 20, 2007 is acknowledged. Claims 1, 3, 22 and 34 (currently amended) and claims 2, 6-15 and 24-33 (original) will be examined on the merits. Claims 4 and 5 have been canceled. Claims 16-21, 23 and 35-44 were previously withdrawn.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/443,471, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The prior application pertains to double-ended sequencing and not bead emulsion nucleic acid amplification. A separate prior application, Application No. 60/465,071, filed April 23, 2003, does

provide adequate support or enablement for the instant application and will be used as the priority date for purposes of examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-3, 6-14, 22, 24, 25, and 30-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Griffiths (U.S. Patent No. 2002/0119459) in view of Wangh et al. (U.S. Patent Pub. No. 2004/0053254).

Griffiths teaches a method for amplifying one or more nucleic acids onto a bead (DNA or RNA in microcapsules can be amplified by various methods, paragraph 23, lines 5-10 and paragraph 98, lines 1-22) comprising the steps of:

(a) forming a water-in-oil emulsion to create a plurality of aqueous microreactors (emulsion has a water phase containing the biomolecules and an inert hydrophobic phase of oil, paragraph 91, lines 14) wherein at least one of the microreactors comprises a single nucleic acid template (microcapsules contain, on average, one or fewer genetic elements each, paragraph 81, lines 1-12 and paragraph 125, lines 1-6), a single bead with a plurality of molecules of a first primer species disposed thereon (one of the PCR primers can be biotinylated and therefore capable of binding to paramagnetic beads coated with avidin, paragraph 110, lines 1-5 and paragraph 111, lines 1-10), wherein the first primer species is capable of binding to the nucleic acid template (nucleic acid may be linked to one or more magnetic beads, paragraph 23, lines 5-10 and paragraph 110, lines 1-5), and amplification reaction solution comprising a plurality of molecules of the first primer species and a second primer species and reagents necessary to perform nucleic acid amplification (NTPs and other necessary reagents are required in the microcapsules for amplification reactions such as PCR, paragraph 98, lines 13-14 and paragraph 100, lines 1-6 and 101, lines 1-8);

(b) amplifying the nucleic acid template in the microreactors using the first and second primer species to form amplified copies of a complementary nucleic acid (DNA or RNA in microcapsules can be amplified by various methods including PCR using one of the primers as a biotinylated primer, paragraph 98, lines 1-22, paragraph 110, lines 1-5 and paragraph 217, lines 1-11); and

(c) capturing said copies on the bead in the microreactor using the first primer species (nucleic acids amplified using biotinylated primers can be captured onto

microbeads coated with avidin, paragraph 110, lines 1-5 and paragraph 111, lines 1-10).

With regard to claim 2, Griffiths teaches a method for amplifying one or more nucleic acids wherein a majority of the microreactors include a single nucleic acid (microcapsules contain, on average, one or fewer genetic elements each, paragraph 81, lines 1-12).

With regard to claim 3, Griffiths teaches a method for amplifying one or more nucleic acids wherein said amplification reaction solution is a polymerase chain reaction solution further comprising nucleotide triphosphates, a thermostable polymerase, and a buffer compatible with polymerase chain reaction conditions (NTPs and other necessary reagents are required in the microcapsules for enzymatic reactions, paragraph 100, lines 1-6 and 101, lines 1-8; PCR can be used if the emulsions are thermostable, paragraph 98, lines 18-23).

With regard to claims 6 and 7, Griffiths teaches a method for amplifying one or more nucleic acids wherein said emulsion additionally contains emulsion stabilizers (emulsions may stabilized by addition of one or more surface-active agents or surfactants such as Span 80, paragraph 92, lines 1-11).

With regard to claims 8 and 9, Griffiths teaches a method for amplifying one or more nucleic acids wherein said emulsion is heat stable to 95°C (emulsions can be made to work under PCR conditions, paragraph 98, lines 18-23).

With regard to claim 10, Griffiths teaches a method for amplifying one or more nucleic acids wherein amplification is carried out by a method of transcription-based

amplification (transcription of the DNA to amplify the nucleic acid copies, paragraph 98, lines 1-12).

With regard to claim 11, Griffiths teaches a method for amplifying one or more nucleic acids wherein the emulsion is formed by the dropwise addition of the nucleic acid templates, beads, and amplification reaction solution into an oil (droplets of microscopic or colloidal size of aqueous phase are added to hydrophobic oil phase, paragraph 90, lines 1-6 and paragraph 91, lines 1-9).

With regard to claims 12 and 13, Griffiths teaches a method for amplifying one or more nucleic acids performed with at least 50,000 nucleic acids (reactions that contain on average one nucleic molecule and one bead (paragraph 23, lines 5-14), contain about 10^9 beads in suspension and therefore as many as 10^9 copies of the nucleic acid, paragraph 300, lines 5-13, paragraph 301, lines 1-4, and paragraph 302, lines 1-2).

With regard to claim 14, Griffiths teaches a method of amplifying nucleic acid in a microreactor such as a water-in-oil emulsion wherein the emulsion droplets range from 0.1 to 10 μm in diameter (paragraph 103, lines 1-6).

With regard to claim 22, Griffiths teaches a method for amplifying a nucleic acid onto a bead comprising the steps of:

(a) providing a nucleic acid template to be amplified (one genetic element is provided in each microcapsule, paragraph 125, lines 1-6);

(b) providing a solid support material comprising a generally spherical bead having a diameter about 10 to about 80 μm, wherein the bead comprises a plurality of molecules of a first primer species disposed thereon capable of binding to the nucleic

acid template (paramagnetic beads containing avidin coating in order to bind nucleic acid are about 5 μm in diameter, paragraph 111, lines 4-10; one of the PCR primers can be biotinylated and therefore capable of binding to the avidin-coated beads, paragraph 110, lines 1-5);

(c) mixing the nucleic acid template and the bead in an amplification reaction solution comprising a plurality of molecules of the first primer species (such as biotinylated primer at allow binding of the products to avidin-coated beads, paragraph 110, lines 1-5), a second primer species and reagents necessary to perform a nucleic acid amplification reaction in a water-in-oil emulsion (microcapsule contains the necessary amplification reagents, paragraph 100, lines 1-6 and is performed in presence of bead, paragraph 111, lines 4-7);

(d) amplifying the nucleic acid template using the first and second primer species to form amplified copies of a complementary nucleic acid (amplification occurs by any number of means including PCR using one of the primers as a biotinylated primer, paragraph 98, lines 1-23 and paragraph 110, lines 1-5); and

(e) capturing said copies on the bead using the first primer species (nucleic acids amplified using biotinylated primers bind to microbeads coated with avidin, paragraph 110, lines 1-5 and paragraph 111, lines 1-10).

With regard to claim 24, Griffiths teaches a method for amplifying one or more nucleic acids further comprising the step of enriching for beads which bind amplified copies of the nucleic acid away from beads to which no nucleic acid is bound, the enrichment step consisting of cell sorting (beads which contain fluorescent signals due

to amplification and subsequent binding of groups involved in generating fluorescent signal can be sorted by flow cytometry, paragraph 202, lines 1-14).

With regard to claim 25, Griffiths teaches a method for amplifying one or more nucleic acids wherein the enrichment step is performed by affinity purification with magnetic beads that bind nucleic acid (enrichment steps can be performed using magnetic beads and a magnet, paragraph 239, lines 34-45).

With regard to claims 30 and 31, Griffiths teaches a method for amplifying one or more nucleic acids wherein amplified copies are bound to the beads by a binding pair such as the ligand/receptor binding pair of biotin and streptavidin, paragraph 111, 1-11).

With regard to claim 32, Griffiths teaches a method for amplifying one or more nucleic acids further comprising the steps of:

separating the template carrying beads and magnetic bead (such as by flow sorting, paragraph 202, lines 1-14; and

removing the magnetic beads with a magnetic field (enrichment steps can be performed using magnetic beads and a magnet, paragraph 239, lines 34-45).

With regard to claim 33, Griffiths teaches a method for amplifying one or more nucleic acids wherein the separating is achieved by incubating the template carrying beads and the magnetic beads in a solution with a basic pH (solution containing beads were suspended in buffer containing 5 mM Tris 7.4 prior to transcription, translation and flow cytometry and incubated at 43°C, paragraph 238, lines 1-10).

Griffiths also does not teach methods of amplifying one or more nucleic acids wherein a concentration of the second primer species is substantially greater than that

of the first primer species in the reaction solution and wherein substantially all of the molecules of the first primer species in the reaction solution are depleted. Griffiths also does not teach microreactors having an average size of 50 to 250 μm in diameter.

Wangh teaches a method of performing non-symmetric PCR using one amplification primer that is present at a concentration at least five times greater than the other primer such that the limiting primer can be used to exhaustion (paragraph 25, lines 1-22 and paragraph 30, lines 1-7). Wangh also teaches a method wherein one of the primers, the limiting one or the primer in excess, is fixed to a solid matrix such as a bead (paragraph 181, lines 1-7).

Wangh does not teach a method for amplifying one or more nucleic acids wherein a bead is contained within a microreactor such as a water-in-oil emulsion wherein amplified copies of the nucleic acid bind to the bead within the emulsion.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Griffiths for amplifying nucleic acids in a microcapsule such as a water-in-oil emulsion on the surface of a bead with the method of Wangh for non-symmetric PCR using primers at unequal concentrations since this method, which causes one of the primers to be used to exhaustion, is highly suited for amplifications that utilize small reaction volumes and very low copy numbers of target sequences (Wangh, paragraph 32, lines 1-8). Furthermore, the assay may be performed in which either of the primers may be attached to a bead, and therefore can be used in the microcapsule format taught by Griffiths. Thus, an ordinary practitioner would have been motivated to use a non-

symmetric PCR assay as taught by Wangh using one of the primers affixed to a bead surface since the assay not only is highly suited for detecting low levels of target sequence, but the extension products will remain attached to the bead (Wangh, paragraph 181, lines 1-7), allowing easy purification of the strand extended from the bound primer for use in other applications such as sequencing. Furthermore, the non-assymetric assay is easily adaptable to performing in microcapsules such as water-in-oil emulsion droplets since such microcapsules are sufficiently large to accommodate any conditions or reaction requirements for amplification reactions such as PCR (Griffiths, paragraph 98, lines 18-23 and paragraph 100, lines 1-6). Moreover, the use of microcapsules allows reactions to be compartmentalized to separate different target sequences from each other, yet targets at very low copy number can still be readily amplified (Griffiths, paragraph 81, lines 1-16).

It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use emulsion droplets of larger sizes such as in the range of 50 μm as used by the applicant or in the range of 10 μm as used by Griffiths since these differences in emulsion droplet size would not be expected to greatly alter the conditions for amplification. Though the effective concentration of a single template DNA would be lower in the larger droplets, this would be offset by the larger absolute amounts amplification reagents such as nucleotides and primers. This is consistent with the Federal Circuit decision in In re Peterson, 65 USPQ2d 1379, 1382 (Fed. Cir. 2003) "We have also held that a prima facie case of obviousness exists when the claimed range and the prior art range do not overlap but are close enough such that one

skilled in the art would have expected them to have the same properties." Thus, an ordinary practitioner would have recognized that the droplet size could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of droplet size was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. As noted, a skilled artisan would expect droplet sizes of 10-50 μm to have nearly identical properties in the amplification of nucleic acids. Thus, an ordinary practitioner would have recognized that the results could be adjusted to maximize the desired results.

6. Claims 15 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (U.S. Patent No. 2002/0119459) in view of Wangh et al. (U.S. Patent Pub. No. 2004/0053254) and further in view of Jurinke et al. (U.S. Patent No. 6,303,309).

Griffiths and Wangh together teach the limitations of claims 1-3, 6-14, 22, 24, 25, and 30-33 as discussed above.

Neither Griffiths nor Wangh teach a method for amplifying one or more nucleic acids wherein at least 1,000,000 amplification copies of each target nucleic acid molecule are bound to each bead. Neither Griffiths nor Wangh teach a method for amplifying one or more nucleic acids wherein the beads are sepharose beads.

Jurinke teaches a method of purification of biotin-labeled PCR products by complexing the products to a solid support containing a biotin-binding compound such as streptavidin immobilized on the surface, including agarose, sepharose, or magnetic beads (column 8, lines 49-60). Jurinke also teaches immobilization of 100 pmol biotinylated oligodeoxynucleotide to 50 μl (~40 million) streptavidin-coated magnetic beads (column 8, 12, lines 13-16), which represents about 1 million molecules bound per bead.

Jurinke does not teach a method for amplifying one or more nucleic acids wherein a bead is contained within a microreactor such as a water-in-oil emulsion wherein amplified copies of the nucleic acid bind to the bead within the emulsion.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Griffiths and Wangh for amplifying nucleic acids on a bead within a microcapsule such as a water-in-oil emulsion using a non-symmetric PCR with that of Jurinke for purification of PCR products using solid-supports such as magnetic or sepharose beads since the use of such beads, because of the stability of the biotin-streptavidin complex, allows further purification and extensive washing to remove all excessive reaction components prior to final recovery of the final PCR product (Jurinke, column 8, lines 61-67). Thus, an ordinary practitioner would have been motivated to use magnetic or sepharose beads as taught by Jurinke for binding and purifying PCR or other amplification products generated in a microreactor since these beads have a large capacity and high affinity

for such products, especially when using highly stable binding pairs such as biotin and streptavidin to form complexes of the amplification products on the beads.

7. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (U.S. Patent No. 2002/0119459) in view of Wangh et al. (U.S. Patent Pub. No. 2004/0053254) and further in view of Nakano et al. (J. Biotech. (2003) 102:117-124).

Griffiths and Wangh together teach the limitations of claims 1-3, 6-14, 22, 24, 25, and 30-33 as discussed above.

With regard to claim 34, Griffiths also teaches a method for producing a clonal population of nucleic acids, comprising:

(a) providing a nucleic acid template to be amplified (one genetic element is provided in each microcapsule, paragraph 125, lines 1-6) and beads each comprising a plurality of molecules of a first primer species disposed thereon capable of binding to the nucleic acid templates (nucleic acid may be bound to beads following PCR using biotinylated primers, paragraph 110, lines 1-5 and paragraph 111, lines 4-10),

(b) mixing the nucleic acid template and the beads in a biological reaction solution that comprises a plurality of molecules of the first primer species (such as biotinylated primer to allow binding of the products to avidin-coated beads, paragraph 110, lines 1-5), a plurality of molecules of a second primer species and reagents necessary to amplify the nucleic acid template (microcapsule contains the necessary amplification reagents for PCR, paragraph 100, lines 1-6 and is performed in presence of bead, paragraph 111, lines 4-7); and

(c) forming an emulsion to create a plurality of microreactors (emulsion has a water phase containing the biomolecules and an inert hydrophobic phase of oil, paragraph 91, lines 14) comprising the nucleic acid template, beads, and the biological reaction solution, wherein at least one of the microreactors comprises a single nucleic acid template (microcapsules contain, on average, one or fewer genetic elements each, paragraph 81, lines 1-12 and paragraph 125, lines 1-6) and a single bead encapsulated in the biological reaction solution (nucleic acid may be linked to one or more magnetic beads, paragraph 23, lines 5-10), wherein the microreactors are contained in the same vessel (such as a microtiter plate or microfuge tube, paragraph 290, lines 1-5 and paragraph 291, lines 1-9).

Neither Griffiths nor Wangh teach a method for amplifying one or more nucleic acids wherein a plurality of nucleic acid templates from 50-800 bp in length are provided.

Nakano teaches a method of PCR in water-in-oil emulsions using a plurality of templates of 528 and 512 bp in size (p. 118, column 2, line 39 to p. 119, column 1, line 8).

Nakano does not teach a method for amplifying one or more nucleic acids wherein a bead is contained within the microreactor and wherein amplified copies of the nucleic acid bind to the bead.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Griffiths and Wangh for amplifying nucleic acids on a bead within a microcapsule such as a water-in-oil

emulsion using a non-symmetric PCR with that of Nakano since Nakano also teaches a method for amplifying multiple nucleic acids in water-in-oil emulsions that is easily adaptable to the methods of Griffiths and Wangh using a bead to bind amplification products in the emulsion. Thus, an ordinary practitioner would have been motivated to use the system of Griffiths and Wangh for amplifying multiple nucleic acid targets of different sizes in an emulsion containing a bead using a non-symmetric PCR process since the products can easily be purified simultaneously on the same bead and later separated by sizing methods or simply analyzed by gel electrophoresis (Nakano, see Figure 2).

Response to Arguments

8. Applicant's arguments filed February 20, 2007 have been fully considered but they are not persuasive.

Applicant argues that the priority date for the instant application should be either April 23, 2003 (for benefit of U.S. Provisional 60/465,071) or January 29, 2003 (for benefit of U.S. Provisional 60/443,471) instead of the previously indicated date of June 6, 2003. Since Application No. 60/465,071, but not No. 60/443,471, provides adequate support for bead emulsion nucleic amplification, the priority date is set as April 23, 2003.

Applicant argues that the 35 USC § 102(a) rejections of claims 1-13, 22, 24, 25 and 30-33 over Griffiths (U.S. Patent Pub. No. 2002/0119459) should be withdrawn since Griffiths no longer teach all the limitations of claim 1 as amended. In particular, Applicant argues that Griffiths does not teach or disclose methods of nucleic acid amplification in microcapsules wherein the concentration of the second primer is

substantially higher than the first primer and wherein the first primer is substantially depleted during the reaction. The Examiner agrees that Griffiths does not teach methods of asymmetric PCR and therefore the 102(b) rejections of claims 1-13, 22, 24, 25 and 30-33 over Griffiths is withdrawn.

However, upon further searching, a new reference was found (Wangh et al. (U.S. Patent Pub. No. 2004/0053254) that teaches methods of non-symmetric PCR in which one of the primers may be linked to a bead. Since this method is useful for PCR amplification of low target copy numbers in small reaction volumes, it is obvious to combine these methods with those of Griffiths for amplification of targets attached to beads in microcapsules. Therefore, claims 1-3, 6-14, 22, 24, 25, and 30-33 are now rejected under 35 USC § 103(a) over Griffiths in view of Wangh. Claim 14, previously rejected under 35 USC § 103(a) over the single reference of Griffiths, is now included in the new 103 rejection, since this claim is dependent on the amended claim 1.

Applicant then argues that the 35 USC § 103(a) rejection of claims 15 and 26-29 over Griffiths in view of Jurinke et al. (U.S. Patent No. 6,303,309) should be withdrawn based on amendments to the claims. In particular, Applicant argues that Griffiths no longer teaches all the limitations of claim 1 as amended. In particular, Applicant argues that Griffiths does not teach or disclose methods of nucleic acid amplification in microcapsules wherein the concentration of the second primer is substantially higher than the first primer and wherein the first primer is substantially depleted during the reaction. Applicant also argues that Jurinke does not make up for this deficiency. As discussed above, claims 1-3, 6-14, 22, 24, 25, and 30-33 are now rejected under 35

USC § 103(a) over Griffiths in view of Wangh since Wangh teaches methods of non-symmetric PCR. Therefore, claims 15 and 26-29 are now rejected under 35 USC § 103(a) over Griffiths in view of Wangh and further in view of Jurinke since it is obvious to use sepharose or magnetic beads capable of binding at least 1 million molecules per bead in the methods of Griffiths and Wangh.

Applicant then argues that the 35 USC § 103(a) rejection of claim 34 over Griffiths in view of Nakano et al. (J. Biotech. (2003) 102:117-124) should be withdrawn based on amendments to the claims. In particular, Applicant argues that Griffiths no longer teaches all the limitations of claim 1 as amended. In particular, Applicant argues that Griffiths does not teach or disclose methods of nucleic acid amplification in microcapsules wherein the concentration of the second primer is substantially higher than the first primer and wherein the first primer is substantially depleted during the reaction. Applicant also argues that Nakano does not make up for this deficiency. As discussed above, claims 1-3, 6-14, 22, 24, 25, and 30-33 are now rejected under 35 USC § 103(a) over Griffiths in view of Wangh since Wangh teaches methods of non-symmetric PCR. Therefore, claim 34 is now rejected under 35 USC § 103(a) over Griffiths in view of Wangh and further in view of Nakano since it is obvious to use the methods of amplification of multiple targets in water-in-oil emulsions as taught by Nakano in the methods of Griffiths and Wangh.

Summary

9. Claims 1-3, 6-15, 22 and 24-34 are rejected. No claims are allowable.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas 5/9/07
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
5/9/07